Category 407

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Categories of Pediatric Research

404: Minimal risk

405: Prospect of direct benefit

406: Minor increase over minimal risk:
"subject's condition requirement"

407: Not otherwise approvable (404-406)

407

- Covers studies which cannot be approved in 404, 405, or 406, for whatever reason.

- Current Focus: more than ‘minimal’ risk research which does not offer the ‘prospect’ of ‘direct’ benefit in healthy children (research is not likely to yield generalizable knowledge about the subjects’ disorder or condition).

407 Requirements

- Expert panel
- Public review
- Opportunity to address a serious problem in children (problem addressed must be a grave one, expected benefit should be significant)
- Consistent with sound ethical principles
- Assent/parental permission

Note: No explicit limit on risk level

Questions

- Is a minor increase over minimal risk acceptable in healthy children? If so, how should it be defined/implemented?
- Are even greater risks ever acceptable?
- What other requirements should be in place to ensure the research is consistent with sound ethical principles?

Potential for Serious Harms

- Some assume the distinction between minimal risk and greater than minimal risk corresponds to the difference between no chance of serious injury and some chance of serious injury.

- This is a mistake: research can pose some chance of serious harm and be minimal risk, if the chance is very low.

Definition

“*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”

Minimal Risk Standards

- Difference between minimal and greater than minimal risk involves exceeding some threshold for typically acceptable risks.

- Different accounts: Risks of daily life or routine procedures; risks we accept in daily life; risks a prudent parent would allow.

Proposed Frame

- Analysis of ‘non-beneficial’ pediatric research, and levels of acceptable risk, needs to recognize the absence of direct benefits to subjects.

- Proposal: non-beneficial pediatric research involves a type of charitable activity for children.

Charitable Risk Standard

- Minimal risk: level of risk acceptable in daily or common activities for children, which are designed to benefit others.

- Minor increase over minimal risk: level of risk posed by exceptional, but still acceptable, activities for children, which are designed to benefit others.

Wendler, Emanuel. J *Pediatrics* 2005; 147:575-578

Determine Risk Level

- First: Do the risks really exceed minimal?
- Studies that pose minimal risk often categorized as greater than minimal.
- Majority of assessed 407 studies posed minimal risk.

Wendler, Varma. *J Pediatrics* 2006; 149:855-861

Data on Minimal Risks

Death: 3 per million

Disability: 40 per million

Broken Bone: 300 per million

Minor Increase Acceptable?

- Minor increase over minimal risk allowed in children with condition under study.
- Risks acceptable in activities designed to benefit others not greater for children with the concern compared to other children (e.g. building houses for the homeless).
- Suggests minor increase over minimal risk acceptable in healthy children.

Priority

- US regulations do not include a “necessity” requirement for pediatric research.
- National Commission attempted to implement this protection in 406 (subject’s condition)
- Should apply to minor increase over minimal risk with healthy children as well: adults first; older children before younger children.

Greater Risks?

- Non-beneficial pediatric research raises greater concern for two primary reasons.
- First, children are not competent.
- Yet, data suggest some older children can understand research to the extent required for valid consent.

Exception #1

- We are assuming that minor increase over minimal risk is acceptable in very young children who cannot understand.
- This suggests somewhat higher risks are acceptable in adolescents who can understand (and agree to participate).

‘Non-direct’ Benefits

- Second concern: non-beneficial pediatric research does not offer the potential for (sufficient) direct benefits.
- Research in this category might offer subjects important non-direct benefits.

G-CSF BMT Study

- 407 panel approved study because it offered donors the opportunity to help a sibling in a very important way.

- This type of ‘non-direct’ benefit might justify more than a minor increase over minimal risk in some cases (in present case, used to approve minor increase over minimal risk in healthy children).

‘Contribution’ benefits

- Claim: contributing to valuable projects typically benefits individuals (i.e. promotes their interests).
- Supported by data that adolescents derive satisfaction and feel proud to participate in research studies to help others.

Level of Contribution Benefits

- Contribution benefits increase with level of individual's authorization and with the value of the study.

- Hence, they may justify somewhat more than minor increase over minimal risk in children who understand the charitable nature of a very valuable study.

Potential for Abuse

- While all benefits are benefits, some less clearly promote individuals' interests, especially for younger children, and have increased potential for abuse.

- Makes sense to limit the possibility of justifying increased risks based on these benefits to special review.

Individual Review

- Special review occurs prior to study initiation.
- Hence, approval is for a class of subjects, not for specific individuals.
- Given concerns, consider evaluation of the risks/benefits for individual children.

Confirmed Permission

- For pediatric studies that raise special ethical concern, important that the parents understand and agree (and the children, if justification depends on their assent).
- Consider requiring (independent?) evaluation of parents, and of children (apart from parents?).

Subject Selection

- Process of choosing who participates especially important for studies which raise greater ethical concern.
- “An equitable method should be used for selecting subjects” (National Commission on 407)
- Both appearance and reality of focusing on specific groups problematic.

Monitoring

- For longitudinal studies, might consider requiring independent monitoring of subjects over time.
- This process could ensure continued willingness to participate and evaluate whether risks greater for some children.

National Commission

"In exceptional circumstances, dangers to children or the community resulting from a failure to involve children in research might exceed whatever risk is presented by that research. For instance, the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable to establish safety, efficacy, and dosage levels for children of different ages. The outright prohibition of such research on grounds of risk might constitute an exception to the general rules enunciated above, however, the decision to permit its conduct should be made at the national level, with opportunity for public participation. In recommendation 6, the Commission suggests procedures by which this goal may be accomplished" (page 128).

National Commission

- “The Commission concluded that promise of substantial benefit does justify research which goes beyond, but only slightly beyond, minimal risk” (page 139).

- Ultimately, the Commission decided (with two members dissenting) that if three conditions are satisfied, research in this most difficult class of cases could be justified (recommendation 5). First, the risk involved must be only a minor increment beyond minimal” (page 139).

National Commission

"The Commission acknowledged that exceptional circumstances may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk…The Commission has chosen to recommend that the ethical argument should be made, not over a hypothetical case, but over an actual situation, in which the real issues and the likely costs of any solution can be more clearly discerned…Thus, Recommendation 6 urges that should such a situation occur, it be defined in the most stringent way and determined by those at high levels of public accountability" (pages 140-141).